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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

WO 2004/100997 A3

(54) Title: SPACER MOIETY FOR POLY(ETHYLENE GLYCOL) -MODIFIED PEPTIDES

(57) Abstract: The present invention relates to a compound comprising a peptide moiety, a spacer moiety and a water-soluble poly-  
mer moiety such as a poly(ethylene glycol) moiety. The spacer moiety is between the peptide moiety and the water-soluble polymer  
moiety. The spacer moiety has the structure: -NH-(CH<sub>2</sub>)<sub>α</sub>-[O-(CH<sub>2</sub>)<sub>β</sub>]<sub>γ</sub>-O<sub>δ</sub>-(CH<sub>2</sub>)<sub>ε</sub>-Y- wherein α, β, γ, δ, and ε are each integers whose  
values are independently selected.

## INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K47/48 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 179 337 A (DAVIS FRANK F ET AL) 18 December 1979 (1979-12-18)  the whole document	1,5,7,9, 10,16, 20,22, 24,25, 33,35
X	WO 00/33881 A (ORSOLINI PIERO ; DEBIO RECH PHARMA SA (CH); CALICETI PAOLO (IT); SCHIA) 15 June 2000 (2000-06-15)  the whole document	1,2,5,7, 9,10,12, 16,17, 20,22, 24,25, 27, 31-33,35

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/014887

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92/16555 A (ENZON INC) 1 October 1992 (1992-10-01)  the whole document	1,2,5,7, 9,10,16, 17,20, 22,24, 25, 31-33,35
X	WO 00/24770 A (AMGEN INC) 4 May 2000 (2000-05-04)  sequence 18	1,5,7,9, 11-13, 16,20, 22,24, 26-28, 30,33,35
X	WO 98/25965 A (GLAXO GROUP LTD ; BALASUBRAMANIAN PALANIAPPAN (US); DEPRINCE RANDOLPH) 18 June 1998 (1998-06-18)  the whole document	1,5,7,9, 11-13, 15,16, 20,22, 24, 26-28, 30,33,35
X	WO 96/40772 A (JOHNSON & JOHNSON ; JOHNSON DANA L (US); ZIVIN ROBERT A (US)) 19 December 1996 (1996-12-19)  the whole document	1,5,7,9, 10, 12-14, 16,17, 20,22, 24,25, 27-29, 33,35
A	WO 96/40750 A (GLAXO GROUP LTD ; GATES CHRISTIAN M (US); JOHNSON SHERRIL S (US); WRIG) 19 December 1996 (1996-12-19) the whole document	
A	WRIGHTON N C ET AL: "INCREASED POTENCY OF AN ERYTHROPOIETIN PEPTIDE MIMETIC THROUGH COVALENT DIMERIZATION" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 15, 1 November 1997 (1997-11-01), pages 1261-1265, XP000749524. ISSN: 1087-0156... the whole document	

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/014887

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GREENWALD R B ET AL: "Effective drug delivery by PEGylated drug conjugates" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 55, no. 2, 10 February 2003 (2003-02-10), pages 217-250, XP002275066. ISSN: 0169-409X the whole document	1-3,5, 10,12, 16-18, 20,25, 27,33,35
X	GREENWALD RICHARD B ET AL: "Controlled release of proteins from their poly(ethylene glycol) conjugates: Drug delivery systems employing 1,6-elimination." BIOCONJUGATE CHEMISTRY, vol. 14, no. 2, 3 April 2003 (2003-04-03), pages 395-403, XP002318263 ISSN: 1043-1802 the whole document	1,2,5-7, 9,10,16, 17,20, 22,24, 25, 31-33,35
A	US 2002/015691 A1 (GREENWALD RICHARD B ET AL) 7 February 2002 (2002-02-07) the whole document	
A	WO 96/40189 A (GLAXO GROUP LIMITED; DOWER, WILLIAM, J; BARRETT, RONALD, W; CWIRLA, ST) 19 December 1996 (1996-12-19) the whole document	
A	WO 00/24782 A (AMGEN INC) 4 May 2000 (2000-05-04) the whole document	
A	US 6 113 906 A (GREENWALD ET AL) 5 September 2000 (2000-09-05) the whole document	
A	WO 02/065988 A (ENZON, INC) 29 August 2002 (2002-08-29) the whole document	
P,X	WO 2004/014424 A (ENZON INC) 19 February 2004 (2004-02-19)  the whole document	1-3,5, 10,12, 16-18, 20,25, 27,33,35
E	WO 2004/101600 A (AFFYMAX, INC; YIN, KEVIN; HOLMES, CHRIS; LALONDE, GUY; BALU, PALANI; T) 25 November 2004 (2004-11-25) the whole document	1-36

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/101606 A (AFFYMAX, INC; YIN, KEVIN; HOLMES, CHRIS; LALONDE, GUY; BALU, PALANI; S) 25 November 2004 (2004-11-25) the whole document -----	1-36
E	WO 2004/101611 A (AFFYMAX, INC; YIN, KEVIN; HOLMES, CHRISTOPHER; LALONDE, GUY; BALU, PAL) 25 November 2004 (2004-11-25) the whole document -----	1-36
E	WO 2004/108070 A (ENZON, INC; ZHAO, HONG; GREENWALD, RICHARD, B) 16 December 2004 (2004-12-16) the whole document -----	1-36

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/014887

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1-36 (partly)**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

**see additional sheet**

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box II.1

The specific specific peptide sequences disclosed in the examples of the present application have, according to PCT Rule 13ter.1.c, not been searched since the Sequence Listing as present in the description does not comply with WIPO Standard ST 25 prescribed in the administrative instructions under Rule 5.2. The Sequence Listing has been furnished neither in paper form nor in machine readable form as provided for in the same instructions and the applicant has not remedied the disclosed deficiencies within the time limit fixed in the invitation pursuant to PCT Rule 13ter.1.a.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: 1,2,5-17, 20-30, 33-36 (all partial), and 31 and 32 (complete)

A conjugate comprising a peptide, a spacer and a water soluble polymer, wherein the spacer moiety is of formula:  $-\text{NH}-(\text{CH}_2)_n-\text{Y}$ . (hence, both  $\gamma$  and  $\delta$  are equal to 0).

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Invention 2: claims 1,2,5-17 and 20-30, 33-36 (all partial), and claims 2-4 and 17-19 (complete)

A conjugate comprising a peptide, a spacer and a water soluble polymer, wherein the spacer moiety is of the formula:  $-\text{NH}-(\text{CH}_2)_a-\text{O}-(\text{CH}_2)_b-\text{O}-\text{d}-(\text{CH}_2)_e-\text{Y}$ , wherein at least one of  $\gamma$  or  $\delta$  is larger than, or equal to, 1, thus forming a spacer having at least one  $-\text{O}-$ .

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/014887

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4179337	A	18-12-1979	CA 1033673 A1	27-06-1978
			CH 616942 A5	30-04-1980
			DE 2433883 A1	05-02-1976
			FR 2313939 A1	07-01-1977
			GB 1469472 A	06-04-1977
			JP 1152589 C	30-06-1983
			JP 50042087 A	16-04-1975
			JP 56023587 B	01-06-1981
			NL 7409770 A	22-01-1975
			SE 441753 B	04-11-1985
			SE 7409366 A	21-01-1975
WO 0033881	A	15-06-2000	EP 1008355 A1	14-06-2000
			AT 283068 T	15-12-2004
			AU 757665 B2	27-02-2003
			AU 1402800 A	26-06-2000
			CA 2354868 A1	15-06-2000
			DE 69922245 D1	30-12-2004
			EP 1137442 A1	04-10-2001
			WO 0033881 A1	15-06-2000
			JP 2002531529 T	24-09-2002
			US 6790942 B1	14-09-2004
WO 9216555	A	01-10-1992	AU 1676992 A	21-10-1992
			CA 2101918 A1	19-09-1992
			EP 0576589 A1	05-01-1994
			JP 6506217 T	14-07-1994
			WO 9216555 A1	01-10-1992
WO 0024770	A	04-05-2000	AU 773891 B2	10-06-2004
			AU 1223900 A	15-05-2000
			BG 105401 A	28-02-2003
			BR 9914698 A	07-01-2003
			CA 2346996 A1	04-05-2000
			CN 1325447 T	05-12-2001
			CZ 20011287 A3	17-10-2001
			EA 3998 B1	25-12-2003
			EP 1124961 A2	22-08-2001
			HU 0104327 A2	28-02-2002
			JP 2002536960 T	05-11-2002
			NO 20011962 A	21-06-2001
			NZ 510529 A	31-10-2003
			PL 348041 A1	06-05-2002
			SK 4962001 A3	03-12-2001
			WO 0024770 A2	04-05-2000
			US 6835809 B1	28-12-2004
			ZA 200102102 A	15-11-2001
WO 9825965	A	18-06-1998	US 5869451 A	09-02-1999
			AU 725731 B2	19-10-2000
			AU 5854798 A	03-07-1998
			BR 9713914 A	29-02-2000
			CA 2274149 A1	18-06-1998
			CN 1245504 A	23-02-2000
			WO 9825965 A2	18-06-1998
			EP 0948539 A2	13-10-1999
			HR 970683 A1	31-10-1998
			JP 2001505898 T	08-05-2001

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/014887

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9825965	A	TR 9901971 T2	21-12-1999
		TR 200401638 T2	22-11-2004
		TW 515804 B	01-01-2003
		US 6121238 A	19-09-2000
		US 6506362 B1	14-01-2003
		ZA 9711045 A	09-06-1999
WO 9640772	A 19-12-1996	US 5767078 A	16-06-1998
		AU 732294 B2	12-04-2001
		AU 6100796 A	30-12-1996
		CA 2228277 A1	19-12-1996
		EP 0892812 A2	27-01-1999
		JP 2000513320 T	10-10-2000
		WO 9640772 A2	19-12-1996
WO 9640750	A 19-12-1996	AU 6046696 A	30-12-1996
		AU 704215 B2	15-04-1999
		AU 6163496 A	30-12-1996
		BR 9608587 A	05-01-1999
		CA 2223449 A1	19-12-1996
		CN 1192749 A	09-09-1998
		CZ 9703897 A3	17-06-1998
		EA 1220 B1	25-12-2000
		EP 0885242 A1	23-12-1998
		HR 960256 A1	28-02-1998
		HU 9900921 A2	28-07-1999
		IL 122102 A	25-07-2002
		JP 3059218 B2	04-07-2000
		JP 10507776 T	28-07-1998
		NO 975705 A	05-02-1998
		NZ 310778 A	28-10-1999
		PL 323917 A1	27-04-1998
		TR 9701526 T1	21-03-1998
		TW 518341 B	21-01-2003
		WO 9640189 A1	19-12-1996
		WO 9640750 A1	19-12-1996
		US 6121238 A	19-09-2000
		US 6251864 B1	26-06-2001
		US 6465430 B1	15-10-2002
		US 5869451 A	09-02-1999
		US 6506362 B1	14-01-2003
		US 6083913 A	04-07-2000
		ZA 9604814 A	09-02-1998
US 2002015691	A1 07-02-2002	NONE	
WO 9640189	A 19-12-1996	AU 6046696 A	30-12-1996
		HR 960256 A1	28-02-1998
		WO 9640189 A1	19-12-1996
		AU 6381896 A	30-12-1996
		EP 0842293 A1	20-05-1998
		WO 9640987 A1	19-12-1996
		AU 704215 B2	15-04-1999
		AU 6163496 A	30-12-1996
		BR 9608587 A	05-01-1999
		CA 2223449 A1	19-12-1996
		CN 1192749 A	09-09-1998
		CZ 9703897 A3	17-06-1998

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/014887

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9640189	A		EA 1220 B1	25-12-2000
			EP 0885242 A1	23-12-1998
			HU 9900921 A2	28-07-1999
			IL 122102 A	25-07-2002
			JP 3059218 B2	04-07-2000
			JP 10507776 T	28-07-1998
			NO 975705 A	05-02-1998
			NZ 310778 A	28-10-1999
			PL 323917 A1	27-04-1998
			TR 9701526 T1	21-03-1998
			TW 518341 B	21-01-2003
			WO 9640750 A1	19-12-1996
			US 6121238 A	19-09-2000
			US 6251864 B1	26-06-2001
			US 6465430 B1	15-10-2002
			US 5869451 A	09-02-1999
			US 6506362 B1	14-01-2003
			US 6083913 A	04-07-2000
			IN 186068 A1	16-06-2001
			ZA 9604814 A	09-02-1998
WO 0024782	A	04-05-2000	US 6660843 B1	09-12-2003
			AU 767725 B2	20-11-2003
			AU 1232200 A	15-05-2000
			BG 105461 A	30-04-2003
			BR 9914708 A	16-07-2002
			CA 2347131 A1	04-05-2000
			CN 1331701 T	16-01-2002
			EP 1144454 A2	17-10-2001
			HU 0203506 A2	28-02-2003
			JP 2003512011 T	02-04-2003
			NO 20011963 A	21-06-2001
			NZ 510888 A	30-01-2004
			SK 5252001 A3	03-12-2002
			WO 0024782 A2	04-05-2000
			US 2004044188 A1	04-03-2004
			US 2004053845 A1	18-03-2004
			US 2004071712 A1	15-04-2004
			US 2004057953 A1	25-03-2004
			US 2004087778 A1	06-05-2004
			US 2004077022 A1	22-04-2004
	ZA 200102753 A	11-06-2002		
US 6113906	A	05-09-2000	US 5919455 A	06-07-1999
			US 5643575 A	01-07-1997
			US 5681567 A	28-10-1997
			US 2002052443 A1	02-05-2002
			AU 743108 B2	17-01-2002
			AU 6463098 A	12-10-1998
			CA 2283939 A1	24-09-1998
			EP 0973819 A1	26-01-2000
			JP 2001519784 T	23-10-2001
			NZ 337845 A	30-03-2001
			WO 9841562 A1	24-09-1998
			AU 8090294 A	22-05-1995
			CA 2174325 A1	04-05-1995
			DE 69427045 D1	10-05-2001
			DE 69427045 T2	25-10-2001

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/014887

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6113906	A		DE 69434046 D1	04-11-2004
			DK 788515 T3	16-07-2001
			EP 1055685 A1	29-11-2000
			EP 0788515 A1	13-08-1997
			JP 9504299 T	28-04-1997
			WO 9511924 A1	04-05-1995
			US 5756593 A	26-05-1998
WO 02065988	A	29-08-2002	CA 2437989 A1	29-08-2002
			EP 1362053 A2	19-11-2003
			JP 2004532289 T	21-10-2004
			MX PA03007392 A	04-12-2003
			WO 02065988 A2	29-08-2002
			US 2002183259 A1	05-12-2002
WO 2004014424	A	19-02-2004	US 2004037802 A1	26-02-2004
			WO 2004014424 A1	19-02-2004
WO 2004101600	A	25-11-2004	WO 2004101600 A2	25-11-2004
WO 2004101606	A	25-11-2004	WO 2004101606 A2	25-11-2004
WO 2004101611	A	25-11-2004	WO 2004101611 A2	25-11-2004
WO 2004108070	A	16-12-2004	US 2005003448 A1	06-01-2005
			WO 2004108070 A2	16-12-2004